TRANSLATION FROM JAPANESE

In 09/770,562

PC9674

Part of #8

(19) JAPANESE PATENT OFFICE (JP)
(11) Unexamined Patent Application (Kokai) No. **2-15027**
(12) Publication of Unexamined Patent Application (A)

(51) Int. Cl.[5]:		Classification Symbols:	Internal Office Registration Nos.:
A 61 K		31/10	ADN 7330-4C
9/16		S 7417-4C	
31/10	ABX		
47/30		B 7417-4C	
47/38		B 7417-4C	

(43) Disclosure Date: January 18, 1990
Request for Examination: Not filed Number of Claims: 1 (Total of 5 pages [in original])

(54) Title of the Invention: **Novel Solid Probucol Preparation**

(21) Application No. 63-162480
(22) Filing Date: July 1, 1988
(72) Inventor: Norihide Doi
(72) Inventor: Naohito Ikuta
(72) Inventor: Hiro Tomizawa
(71) Applicant: Takada Seiyaku KK
(74) Agent: Tadao Minami, Patent Attorney

SPECIFICATION

1. Title of the Invention

Novel Solid Probucol Preparation

2. Claims

A solid probucol preparation, characterized in that one or more enterically or intestinally soluble polymer compounds selected from the group consisting of an aminoalkyl methacrylate copolymer E, a methacrylic acid copolymer L, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, polyvinyl acetal diethylaminoacetate, and hydroxypropylmethyl cellulose phthalate is or are milled together with probucol, and the resulting fine powder composition is made into a preparation.

3. Detailed Description of the Invention

Field of Industrial Application

The present invention relates to a novel solid probucol preparation which is useful as a medicinal product, and is in particular intended to provide a preparation with improved bioavailability, which is achieved by using a specific technique for producing a preparation in order to enhance the solubility of probucol, a medicinal substance that is poorly water soluble.

Prior Art

Probucol, which has been shown to have action in improving hypercholesterolemia induced in animals, has been put to practical use as a serum lipid improver since 1977 in North America and since 1985 in Japan. Clinical studies in Japan have shown it to have far better action than similar drugs in reducing total cholesterol in serum. However, probucol is poorly soluble in water, seriously compromising its elution from preparations produced by common techniques for producing solid preparations, such as techniques for producing granules or tablets with the addition of excipients and the like. A major drawback is thus its inability to be rapidly absorbed

via the intestinal tract. Examples of common means for improving the elution of poorly soluble medicinal substances include:

A) converting such substances to a solubilizable substance, and using the resulting derivative; and

B) adding a dissolving aid such as a surfactant while producing the preparation.

These generally used options, unfortunately, have failed to produce satisfactory results with probucol.

More specifically, solubilizable derivatives suitable for practical use have yet to be developed. Finely powdered products have failed to achieve this objective, while there has been little success with the use of surfactants commonly used as elution aids, such as Polysorbate 80, sodium laurylsulfate, and Polyoxyl 40 stearate. Although the use of large amounts of such substances has resulted in substances capable of such effects for experimental purposes, the products are not suitable for practical use. One technique that has been considered is to dissolve the material in a dissolving agent such as polyethylene glycol 400 or propylene glycol for subsequent preparation in the form of soft capsules, but the large product that results has proven to be a problem (large capsules and tablets are difficult to swallow).

Disclosure of the Invention

As a result of extensive research intended to improve the elution of solid probucol preparations, the inventors succeeded in providing a solid probucol preparation with better elution by milling one or more enterically or intestinally soluble polymer compounds selected from the group consisting of an aminoalkyl methacrylate copolymer E, a methacrylic acid copolymer L, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, polyvinyl acetal diethylaminoacetate, and hydroxypropylmethyl cellulose phthalate together with probucol to produce a fine powder composition, which is then made into a preparation.

That is, the present invention is intended to provide a solid probucol preparation, characterized in that one or more enterically or intestinally soluble polymer compounds selected from the group consisting of an aminoalkyl methacrylate copolymer E, a methacrylic acid

copolymer L, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, polyvinyl acetal diethylaminoacetate, and hydroxypropylmethyl cellulose phthalate is or are milled together with probucol, and the resulting fine powder composition is made into a preparation.

The present invention is described in further detail below.

The enterically soluble polymer compound used in the solid preparation of the present invention is selected from the group consisting of an aminoalkyl methacrylate copolymer E and polyvinyl acetal diethylaminoacetate. The intestinally soluble polymer compound is selected from the group consisting of a methacrylic acid copolymer L, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, and hydroxypropylmethyl cellulose phthalate.

These polymer compounds can be used alone or in combinations of two or more. They are used in an amount of at least 0.1 time, and preferably 0.5 to 10 times, by weight, the amount of the probucol. They are milled with the probucol to produce a fine powder composition.

A water-soluble saccharide such as glucose, fructose, mannitol, sorbitol, xylitol, maltose, lactose, and sucrose, or a sugar alcohol, can be used as an excipient when preparing such a fine powder composition. This will facilitate the milling treatment. The type of mill and the time for which the milling treatment is undertaken are not particularly limited.

The resulting fine powder composition can then be made into a variety of solid preparations using common methods for producing solid preparations. That is, excipients, disintegrants, binders, lubricants, and the like can be added to the fine powder composition to produce dispersions, subtilized granules, granules, capsules, tablets, and the like in the usual manner.

Preparations of the present invention produced with the milling treatment described above will have better probucol solubility and far better bioavailability. The probucol preparation can thus be provided in the form of smaller capsules and tablets.

Examples of the present invention are given below along with test examples and comparative examples to further illustrate the present invention.

Parts in the following examples are based on weight.

Comparative Example 1

A commercially available product containing 250 mg probucol per tablet was ground with a mortar and pestle to produce granules.

Example 1

The following composition was used.

probucol	10 parts
lactose	10 parts
aminoalkyl methacrylate copolymer E	10 parts
carboxymethyl cellulose	3 parts
magnesium stearate	1 part

The probucol, lactose, and aminoalkyl methacrylate copolymer E were thoroughly mixed and then milled together for 30 minutes in a vibrating rod mill (model TI-200, by Heiko Seisakusho) to produce a fine powder composition with a mean particle diameter of no more than 10 μm. The carboxymethyl cellulose and magnesium stearate were then added to the fine powder composition, and the ingredients were thoroughly mixed and then dry granulated, yielding granules.

Example 2

probucol	10 parts
lactose	10 parts
methacrylic acid copolymer L	10 parts
carboxymethyl cellulose	3 parts
magnesium stearate	1 part

The probucol, lactose, and methacrylic acid copolymer L were thoroughly mixed and then milled together for 30 minutes in a vibrating rod mill to produce a fine powder composition with a mean particle diameter of no more than 10 μm. The carboxymethyl cellulose and magnesium

stearate were then added to the fine powder composition, and the ingredients were thoroughly mixed and then dry granulated, yielding granules.

Example 3

probucol	10 parts
lactose	10 parts
cellulose acetate phthalate	10 parts
carboxymethyl cellulose	3 parts
magnesium stearate	1 part

The probucol, lactose, and cellulose acetate phthalate were thoroughly mixed and then milled together for 30 minutes in a vibrating rod mill to produce a fine powder composition with a mean particle diameter of no more than 10 μm. The carboxymethyl cellulose and magnesium stearate were then added to the fine powder composition, and the ingredients were thoroughly mixed and then dry granulated, yielding granules.

Test Example 1 (Dissolving Test)

Sample (1) probucol fine powder

Probucol was milled for 1 hour in a vibrating rod mill to produce a fine powder with a mean particle diameter of no more than 10 μm.

Sample (2) fine powder composition comprising equal amounts of probucol and lactose

Equal amounts of probucol and lactose were milled for 1 hour in a vibrating rod mill to produce a fine powder with a mean particle diameter of no more than 10 μm.

Sample (3) fine powder composition comprising equal amounts of probucol, lactose, and aminoalkyl methacrylate copolymer E

Equal amounts of the three components were mixed and then milled for 1 hour in a vibrating rod mill to produce a fine powder with a mean particle diameter of no more than 10 μm.

Sample (4) fine powder composition comprising equal amounts of probucol, lactose, and methacrylic acid copolymer L

Equal amounts of the three components were mixed and then milled for 1 hour in a vibrating rod mill to produce a fine powder with a mean particle diameter of no more than 10 μm.

Sample (5) fine powder composition comprising equal amounts of probucol, lactose, and cellulose acetate phthalate

Equal amounts of the three components were mixed and then milled for 1 hour in a vibrating rod mill to produce a fine powder with a mean particle diameter of no more than 10 μm.

Samples (1) through (5) were precisely weighed out in amounts corresponding to 20 mg probucol, and purified water was added to bring the total to precisely 100 mL. The mixtures were dispersed (90 to 100 cycles per minute; horizontal reciprocating shaking) for 1 hour at 37°C in shaking thermostatic water tanks (Lab Thermoshaker TS-30G, by Advantech). The dispersions were filtered with a membrane filter having a pore diameter of 0.45 μm, and the optical resolution of the filtrate was measured at a maximum absorption wavelength near 240 nm to determine the amount of probucol that had been dissolved (μg/mL). The results are given in Table 1.

Table 1: Dissolving test

Sample	Amount dissolved (μg/mL)	
(1) probucol fine powder	purified water	0.13
(2) fine powder composition comprising equal amounts of probucol and lactose	purified water	0.20
(3) fine powder composition comprising equal amounts of probucol, lactose, and aminoalkyl methacrylate copolymer E	purified water	0.13
	first liquid	8.58
(4) fine powder composition comprising equal amounts of probucol, lactose, and methacrylic acid copolymer L	purified water	0.19
	second liquid	6.43
(5) fine powder composition comprising equal amounts of probucol, lactose, and cellulose acetate phthalate	purified water	6.78
	second liquid	53.10

Table 1 shows that the fine powder compositions used in the preparation of the present invention resulted in far higher dissolved amounts than the fine powder of probucol alone or the fine powder of probucol and lactose.

Test Example 2

The granules of Comparative Example 1 and Examples 1 through 3 were orally administered in amounts corresponding to 1 g probucol per animal to four white Japanese rabbits weighing about 3 kg. The concentration in plasma (μg/mL) 4 through 48 hours after administration, the maximum concentration in plasma (Cmax (μg/mL)), and the area under curve of the plasma concentration vs. time (AUC (μg-hr/mL)) were determined.

The results are given in Tables 2 and 3.

Table 2: Concentration in plasma (μg/mL)

Time / Sample	4 hr	8 hr	12 hr	16 hr	20 hr	24 hr	28 hr	32 hr	48 hr
Comp. Ex. 1	0.114	0.099	0.081	0.094	0.099	0.103	0.098	0.090	0.108
Ex. 1	0.292	0.713	0.745	0.970	1.204	1.149	1.144	1.066	1.045
Ex. 2	0.909	1.610	1.417	1.400	1.537	1.533	1.457	1.604	0.992
Ex. 3	0.203	0.303	0.475	0.387	0.381	0.385	0.533	0.535	0.330

Table 3: Maximum plasma concentration, and AUC

Index / Sample	Cmax (μg/mL)	AUC (μg-hr/mL)
Comparative Example 1	0.114	7.272
Example 1	1.204	87.063
Example 2	1.610	102.084
Example 3	0.535	28.371

Tables 2 and 3, and Figure 1 , show that the solid preparations of the present invention resulted in far higher levels in plasma than the preparation of the comparative example.

As noted above, the solid preparation of the present invention is characterized by higher probucol elution and far better bioavailability.

4. Brief Description of the Drawings

Figure 1 is a graph of the test results in the animal experiment of Test Example 2.

Figure 1